REJECTION UNDER 35 U.S.C. § 102 OVER DÜRING

The rejection of claims 21, 32-39, 42-47, 49-54, 56, 57, 60-66, 68, 70-75, 78, and 80-82 under 35 U.S.C. § 102(b) as being allegedly anticipated by the During Dissertation is respectfully traversed.

Claims 43 and dependents are not anticipated by During

During fails to disclose or otherwise teach the elements of claim 43 and its dependent claims including the requirement for a plant comprising plant cells containing nucleic acid encoding an immunoglobulin single polypeptide product. As noted by Lerner, "I could find nothing in the During dissertation that addresses expression of a single polypeptide form of immunoglobulin, such as an sFv fragment." *Id.* It was the inventors of the above-captioned patent application, not During, who were the first describe assembly of an antigen-specific sFv in plant cells. Thus, on this basis alone, the During dissertation does not anticipate claim 43 and its dependent claims.

Furthermore, the strategy used by During for light and heavy chain expression is different from that which underlies the claimed invention, in particular, the requirement for nucleic acid to encode a heavy and light chain along with a leader sequence for each chain, and the requirement for production of antigen immunoglobulin product encoded by the nucleic acid, which requires the leader sequence forms a secretion signal that is cleaved from the immunoglobulin polypeptide (heavy or light chain or H/L single polypeptide) following proteolytic processing. According to the During dissertation, the nucleic acid encoding the barley alpha amylase signal sequence was inserted directly 5' to the end of the DNA encoding the amino terminal end of the mature heavy chain. In the case of the light chain, however, During included nucleic acid encoding three additional amino acids (Gly-Ser-Met) between the DNA encoding the leader sequence and the DNA encoding the mature amino terminus of the light chain. Lerner declaration, ¶9. The additional amino acids that would be encoded at the 3' end of the light chain leader sequence constructed by During were unusual, according to Lerner, and it was not clear what effect additional amino acids would have on final processing of the leader. Lerner declaration, ¶¶10 and 11. In is now clear from the art that mutations introduced in the

vicinity of a cleavage site have the potential to adversely influence signal processing. Lerner declaration, ¶11. In the opinion of Lerner, During's strategy of adding additional amino acids residues to the cleavage site for the light chain leader likely obscured substrate recognition causing cleavage site ambiguity. Lerner declaration, ¶¶11 and 12.

Thus, it is respectfully submitted that these facts alone evidence that the During dissertation does not teach the claimed requirement for proteolytic processing of a leader sequence and assembly of the heavy and light chains to form an antigen-specific immunoglobulin in the plant cell. It is respectfully submitted, therefore, that no substantive foundation exists upon which to find the claims anticipated (or obvious) over During and the rejection fails on this basis alone.

B. The claims are not anticipated (or obvious) because During's assertion of successful antibody expression in plants would not have been believed by the ordinary skilled artisan or, in the alternative, the During dissertation is non-enabling.

1. <u>There was a prejudice in the art against the possibility that plant cells could be used to produce an antigen-specific immunoglobulin</u>

Any analysis of the of the prior art in the context of an anticipation or obviousness rejection must be made from the perspective of the ordinary skilled artisan at the proper time frame. The Lerner declaration goes to great length to properly ascertain this perspective at the time period beginning from the alleged publication date of the During dissertation (July 1988) and up to the earliest filing date of the above captioned patent application (October 27, 1989). The analysis shows that there is strong evidence at the relevant time period for the existence of a prejudice in the art against the possibility of using plant cells to process and assemble an antigen-specific immunoglobulin. According to Lerner, it was appreciated by the early 1980s that the biology of antibody expression was complex and varied with the maturation state of the B cell. For example, rearrangement of immunoglobulin chain variable region encoding gene segments is required to form a functional immunoglobulin gene, and rearrangement of the heavy chain

occurs before rearrangement of the light chain. In fact, there is an early stage B cell known as the "pre-B cell," characterized in having a productively rearranged heavy chain V gene but not a rearranged light chain V gene. Lerner declaration, ¶3. In contrast, a later stage of B cells is known ("young B cell), characterized in having both the heavy and the light chain V genes productively rearranged and in expressing a full-sized immunoglobulin on the cell surface. *Id.*

Lerner goes on to explain that antibody expression in B cells was understood to be further complicated by the involvement of the BiP protein, known to be involved in heavy chain processing. Lerner declaration, ¶3. A phenomenon called heavy chain toxicity also was appreciated at the time but its mechanism was unknown. Lerner declaration, ¶4. According to Lerner, by the mid 1980s, a prejudice had taken hold in the art against the notion that antigen-specific immunoglobulins could be produced in cells other than mammalian B cells. *Id.*

Although Lerner notes the existence of reports describing expression of an assembled antibody in two microorganisms (i.e., *Saccharomyces cerevisiae* and *E. coli*) he provides substantial reasoning for why the prevailing prejudice in the art would still have existed with respect to producing antigen-specific immunoglobulin in plant cells. Lerner declaration, ¶7. For example, Lerner notes that plant cells were known to be different from mammalian cells and from microorganisms such as *Saccharomyces cerevisiae* and *E. coli* not only in having a cell wall but also in features related to protein secretion. In addition, Lerner notes that it was not known at the time whether plant cells contained a BiP protein or a functionally equivalent analogue. Lerner concludes from his review of the field that:

> [T]here was a sound basis for a real prejudice in the art against using plants to produced a processed and assembled immunoglobulin which is antigen specific around the time of the During dissertation (*circa* 1988/1989). Were this not the case, then Applicant's invention clearly would not have been roundly hailed in both the scientific literature and in the general press as a significant scientific discovery and medical breakthrough.

Lerner declaration, ¶8 (footnotes removed). It stands to reason, therefore, that the ordinary skilled artisan in the 1988/1989 time frame would have applied this prejudice to any claim purporting to demonstrate processing and assembly of an antigen-specific immunoglobulin in plant cells and would not have accepted such claim unless the proof was well founded. It is respectfully submitted that the teachings of the During declaration with respect to the rejection, must be viewed in light of this prejudice.

2. During's experimental results supporting immunoglobulin expression are internally inconsistent and are lacking in critical controls

During initially made a light chain only expression vector and evaluated whether plant cells transfected with this vector could express light chains. During, however, failed to detect light chain production in the cells (During dissertation, p. 80, line 2). According to Lerner, this fact would have been disturbing to the ordinary skilled artisan because light chain alone is readily expressed in B cells, and even if During's cells were making a small amount of light chain, albeit at a level below his detectability limit, this would complicate efforts to achieve and detect heavy-light chain assembly. Lerner further points out that an increased relative heavy chain expression, which under the circumstances might be necessary to obtain assembly in view of the low levels of expressed light chain, conceivably could result in toxicity if plant cells were susceptible to heavy chain toxicity, as was the case for mammalian B cells. These issues would have raised serious questions about During's chances for success and would have required additional proof for any alleged success to be accepted in the art.

Although During appreciated that his expression system was suboptimal, he proceeded to attempt expression of both a heavy and light chain from a single expression vector. Anticipating a threshold detectability problem, During utilized a pre-enrichment step prior to Western blotting (i.e., indirect Western) of transgenic plant extracts. Lerner declaration, ¶14. Lerner points out that During's need for an indirect Western also would have been disturbing to the ordinary skilled artisan because direct Western blotting was known to be a very sensitive technique had previously been successfully used to

demonstrate foreign host expression (including plant expression of antibodies as disclosed in the instant patent application). *Id.*

The Examiner is referred to the Lerner declaration § 15 for details of During's indirect Western results. It is significant that During now observes light chain detection with the dual chain vector (but not with the light only vector used earlier) but was unable to detect heavy chains by either direct or indirect Western blotting. *Id.* During's assertion that he has detected the presence of assembled B1-8 antibody in the plant cells is based, according to Lerner, on faulty circular logic.

> To conclude as he does from the Western results that assembled B1-8 antibody was present in the plant extract, During must infer that which he is attempting to prove, that fully assembled antibody must have been present in the extract for light chain to have been enriched following binding to the NP hapten immunoabsorbent. As will be seen below, this faulty circular reasoning is open to alternative explanations that directly conflict with During's conclusion.

Lerner declaration, ¶ 15. Lerner goes on to discuss numerous other reasonable explanations for the results that During did not address, let alone attempt to exclude. Notably, During fails to exclude the real possibility that light chain may have been enriched by the NP immunoabsorbant even if the light chain were not assembled with a heavy chain. During's failure to detect heavy chains by direct and indirect Western blotting is consistent with this possibility. As summarized by Lerner, there was much that During could have done (but failed to do) to exclude alternative artifactual explanations for his Western blotting data.

> For example, During could have directly demonstrated that heavy chain was absolutely required for light chain binding during the pre-enrichment step. Alternatively, or in addition, During could have used biosynthetic radiolabeling of plant cells in combination with Western blotting to prove that a heavy chain was in fact co-enriched with light chain. This method is well known in the art and was previously used to demonstrate foreign protein expression. Biosynthetic radiolabeling also helps to control for stripping of antibody during a low pH elution of an antibody immunoabsorbent column (i.e., the Ls136 adsorbent), a problem encountered with CNBr. Since

> During employed low pH elution and CNBr linkage, he should have provided controls to address this potential problem.

Lerner declaration, ¶ 16 (footnotes removed).

The During dissertation also evaluated antibody expression in his plants using a second technique referred to as "tissue printing." In this technique, a leaf is pressed against a membrane in order to bind proteins in the leaf to the membrane, and the membrane is probed by immunological reagents as in Western blotting. The During dissertation describes that light chain, heavy chain and "aggregated B1-8" antibody were detected by tissue printing. Although During asserts that these results support his conclusion of successful immunoglobulin assembly, Lerner believes that the tissue printing experiment are just as readily subject to alternative explanations because they lack controls which are essential to conclude that binding of an immunological reagent is antigen-specific. Lerner declaration, ¶ 17. Lerner bases his belief not only on his own experience as a scientist and immunologist for more than 30 years but also on the scientific literature. With respect to the latter, Lerner points out that the types of controls lacking in the During dissertation were used by others who previous to During demonstrated expression in yeast of the same B1-8 antibody that During was attempting to express in a plant. *Id.* (referring to Wood et al.) The few controls used by During in the tissue printing experiments were wholly insufficient under the circumstances to support During's assertion of success.

The During dissertation also includes immunogold electron microscopic analysis of his transgenic plant cells apparently with the same antibodies used in the Western blotting and tissue printing experiments. The Examiner is referred to the Lerner declaration § 18 for a detailed explanation of During's immunogold results. Lerner takes issues with During's conclusion that the immunogold results indicate successful assembly of the B1-8 antibody in plants. First, Lerner notes that the heavy chain again was not detected and because areas of the cell that were immunogold labeled with the light chain reagent were not the same areas that were immunogold labeled with the Ac38 reagent (allegedly specific for assembled B1-8). Lerner declaration, ¶ 18. It stands to reason that for assembly to have occurred, the two chains should be co-localized to at least one area of

the cell. Furthermore, During failed to observe immunogold labeling in regions of the cell that one would normally have expected if antibody assembly were possible in plant cells. Lerner declaration, ¶ 19. Indeed, During observed immunoreactivity inexplicably in chloroplasts with the Ac38 antibody but not in the golgi apparatus or vesicles as others have observed previously for secreted proteins including antibodies. Unusual results might be acceptable if plant cells were capable of antibody assembly in unique and previously unknown ways, however, unusual results cannot make up for the lack of controls in other experiments.

Lerner concludes that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed the assertion of the During dissertation that plant cells could be used to process and assemble an antigen-specific immunoglobulin. Lerner declaration, ¶ 22. Lerner bases this belief on During's failure to perform critical controls to support his conclusions and to explain his inconsistent results. Also, the Ac38 antibody which underlies virtually all of the support for During's assertion cannot be used, according to Lerner, to prove that NP antigen specific binding was present in plant cells. Lerner declaration, ¶ 22. Thus, even if During had done the proper antigen inhibition controls, more would have been needed, according to Lerner, to overcome the prejudice in the art. *Id.*

It is also Lerner's opinion that even if there were no prejudice in the art, During's conclusions would still not have been accepted. This view is based in part on Lerner's extensive experience as an editorial board member of more than ten scientific journals and an official reviewer for hundreds articles submitted for publication. Although During eventually published his antibody work in a peer-reviewed journal (i.e., Plant Molecular Biology), this occurred after the inventors of the above-captioned application published their work (1989 Nature article). Furthermore, as noted by Lerner, During's publication discusses the earlier publication by the inventors Hiatt and Hein at some length, describing it as a successful demonstration of antibody expression in plants. Lerner declaration, ¶ 22. In Lerner's opinion, had During not been able to support his work with the earlier publication by Hiatt and Hein, During's antibody expression experiments most likely would

have been deemed unacceptable for publication. Lerner credits the inventors of the instant patent application, not During, as the first to convincingly demonstrate assembly of an antigen-specific immunoglobulin in plant cells.

The teachings of the During dissertation are equally if not more defective with respect to expressing an antigen-specific single polypeptide form of immunoglobulin in plants. The heavy chain variable region of the single polypeptide must assemble with the light chain variable region portion in order to achieve an antigen specific immunoglobulin. Lerner declaration, ¶ 24. Furthermore, as noted by Lerner, "I could find nothing in the During dissertation that addresses expression of a single polypeptide form of immunoglobulin, such as an sFv fragment." *Id.* It was the inventors of the above-captioned patent application, not During, who were the first describe assembly of an antigen-specific sFv in plant cells.

Claims 83 and dependents are not anticipated by During

As already described, During tried but failed to express a light chain polypeptide without the heavy chain (During dissertation, p. 80, line 2) and During made no attempt to express a heavy chain polypeptide without a light chain polypeptide. Thus, During does not disclose the requirement for nucleotide sequence to encode an immunoglobulin single polypeptide product containing an immunoglobulin heavy chain polypeptide or an immunoglobulin light chain <u>but not both</u>. Applicant's position is supported by the Lerner declaration which credits expression of a antigen-specific single polypeptide immunoglobulin in plants to the instant inventors, not During.

> The During dissertation also fails to teach how to successfully use plant cells to express a heavy chain or light chain polypeptide, but not both, in plant cells. As already discussed, During attempted light chain expression without the heavy chain (but not vice versa) but failed to detect light chains in the plant cells. During did not even attempt to express heavy chains by themselves in plant cells. In contrast, the inventors of the above-captioned patent application, were the first describe that plant cells can express the light chain or the heavy chain separately in a plant cell. In my opinion, the ability of plants to express each individual chain (light or heavy) was unexpected, particularly in the case

> of the heavy chain which was known at least in mature B cells to cause toxicity when expressed without a light chain.

Lerner declaration, ¶ 25. On this basis alone, the During dissertation fails to anticipate claim 83 and its dependent claims.

The During dissertation also does not disclose the claimed requirement for a plant cell the heavy chain alone or the light chain alone wherein each such chain could assemble into an antigen-specific immunoglobulin if expressed in the same cell with the other of the chain. The same arguments above for claims 43 and dependents apply equally well here. Accordingly, these additional grounds constitute an independent basis on which to find that claims 83 and its dependent claims are not anticipated by the During dissertation.

Accordingly, because the During dissertation fails to disclose each and every element of the claimed invention, claim 43 and its dependent claims and claim 83 and its dependent claims are not anticipated under section 102(b) as a matter of law.

REJECTION UNDER 35 U.S.C. § 102 OVER GOODMAN

The rejection of claims 21, 32-40, 42-47, 49-54, 56-58, 60-66, 68, 70-76, and 78-82 under 35 U.S.C. § 102(e) as being allegedly anticipated by Goodman (U.S. No. 4,956,282) is respectfully traversed.

Claim 43 and its dependents are not anticipated by Goodman

Goodman fails to disclose or otherwise teach the elements of claim 43 and its dependent claims including the requirement for a plant comprising plant cells containing nucleic acid encoding an immunoglobulin single polypeptide product. This is readily evident because Goodman makes only a passing reference to expressing immunoglobulins, which is nearly buried amidst a laundry list of known mammalian proteins as seen below:

> Structural genes of interest include .alpha.-, .beta.- and .gamma.-interferons, **immunoglobulins, with the structural genes coding for the light and heavy chains and desirably assembly occurring in the plant cell**, lymphokines, such as interleukins 1, 2 and 3, growth factors, including insulin-like

> growth factor, epidermal growth factor, platelet derived growth factor, transforming growth factor-.alpha., -.beta., etc., growth hormone, insulin, collagen plasminogen activator, blood factors, such as factors I to XII, histocompatibility antigens, enzymes, or other mammalian proteins, particularly human proteins.

U.S. No. 4956282, col. 3, lines 11-30 (emphasis added). There is clearly nothing in this statement that refers directly or indirectly to an immunoglobulin single polypeptide product that includes the light and the heavy chain. On this basis, Goodman clearly cannot anticipate claim 43 and its dependent claims.

Claim 83 and its dependents are not anticipated by Goodman

Goodman's passing reference to an immunoglobulin misses entirely the idea of preparing plant cells containing nucleotide sequence encoding an immunoglobulin single polypeptide product containing an immunoglobulin heavy chain polypeptide or an immunoglobulin light chain but not both. On this basis, Goodman clearly cannot anticipate claim 83 and its dependent claims. Furthermore, Goodman never attempted to express immunoglobulin in a plant. Goodman's statement to expressing immunoglobulin amounts to nothing more than a unsupported wish to express every type of commercially useful protein in plants.

Accordingly, because Goodman fails to disclose each and every element of the claimed invention, claim 43 and its dependent claims and claim 83 and its dependent claims are not anticipated under section 102(b) as a matter of law.

REJECTION UNDER 35 U.S.C. § 103 OVER DÜRING

The rejection of claims 21, 32-54, 56-66 and 68-82 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Düring in view of Applicant's allegedly admitted prior art is respectively traversed.

Relevant Law

A claimed invention is obvious if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103 (1994); see also Graham v. John Deere, 383 U.S. 1, 13 (1966). Federal Circuit case law provides that "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." In re Dow Chem., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988). Under the law, there must be a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential evidentiary component of an obviousness holding." C.R. Bard, Inc. v. M3 Sys. Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed.Cir.1998). Also required is that the combined teachings have a reasonable expectation of success, viewed in light of the prior art. *See* In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988)("Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure.").

The examiner bears the burden of establishing a *prima facie* case of obviousness. In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed.Cir.1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed.Cir.1992). This showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not "evidence." *See* Dembiczak, 175 F.3d at 1000, 50 USPQ2d at 1617. However, the suggestion to combine need not be express and "may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Technology Corp., 121 F.3d 1461, 1472, 43 USPQ2d 1481, 1489 (Fed.Cir.1997). Only when the examiner's burden is met does the burden of coming forward with rebuttal argument or evidence shift to applicant. Rijckaert, 9 F.3d at 1532, 28 USPQ2d at 1956.

Claim 43 and its dependents are not bvious over During

To reiterate, claim 43 and its dependents require plant cells containing nucleotide sequences each encoding an immunoglobulin single polypeptide product containing at least an immunoglobulin heavy chain polypeptide or portion thereof and an immunoglobulin light chain or portion thereof. The claim further requires the plant cells to contain immunoglobulin single polypeptide product encoded by the nucleotide sequences, wherein the leader sequence is cleaved from said the polypeptide product following proteolytic processing.

As already discussed under anticipation, the During dissertation fails to disclose or otherwise teach a plant comprising plant cells containing nucleic acid encoding any immunoglobulin single polypeptide product. During in fact arguably teaches away from the claimed invention because During attempted **and failed** to express an immunoglobulin light chain polypeptide by itself. During dissertation translation, p.80, line 2. Moreover, During never attempted expression of the immunoglobulin heavy chain polypeptide by itself. During never even discussed expressing a single polypeptide immunoglobulin that has a heavy and a light chain such as a single chain Fv fragment. Even for what it purports to teach, as discussed above under the rejection for anticipation, the During dissertation would either not have been convincing or would have been considered a non-enabling disclosure. Thus, the teachings of the During dissertation would be even more deficient when considered in regards to a form of immunoglobulin that the reference does not even discuss.

It is respectfully submitted, therefore, that the above noted deficiencies in the teachings of the During dissertation demonstrate overwhelmingly that no substantive foundation exists upon which to find claims claim 43 and its dependents obvious over this reference.

Although the claims have not presently been rejected as obvious over the During dissertation in combination with any specified prior art teaching, it is also respectfully submitted that no such teachings or combination of teachings have been cited in this case

that could cure the deficiencies noted for During. The only other reference raised for obviousness in this action is Goodman, but the teachings of this reference are similarly deficient to that of the During dissertation. When it comes to immunoglobulins, Goodman only mentions expressing immunoglobulin heavy and light chains together in the same cell so that the chains can assemble. Such immunoglobulin, however, clearly does not teach or suggest the invention of claim 43 and its dependents.

Claim 83 and its dependents are not obvious over During

To reiterate, claim 83 and its dependents require plant cells containing nucleotide sequence encoding an immunoglobulin heavy chain polypeptide or an immunoglobulin light chain but not both. In this claim the heavy chain or light chain are from an antigen-specific immunoglobulin, and the single polypeptide product is capable of forming an antigen-specific immunoglobulin when co-expressed in the same cell with the other chain of the antigen-specific immunoglobulin. Claim 83 is intended to cover transgenic plants which separately express either the heavy chain or the light chain of an antigen-specific immunoglobulin. As described in the instant application, such plants can be crossed to yield a plant with plant cells that express both the heavy and light chains which assemble in the plant cell to form an antigen specific immunoglobulin.

As discussed, the During dissertation is wholly deficient with respect to teaching a plant comprising plant cells containing nucleic acid encoding any immunoglobulin single polypeptide product. During in fact teaches away from the claimed invention because During attempted **and failed** to express an immunoglobulin light chain polypeptide by itself and never attempted expression of the immunoglobulin heavy chain by itself. During dissertation translation, p.80, line 2. Even for what it purports to teach, as discussed above under the rejection for anticipation, the During dissertation would either not have been convincing or would have been considered a non-enabling disclosure. Thus, the teachings of the During dissertation would be even more deficient when considered in regards to a form of immunoglobulin that the reference does not even discuss.

It is respectfully submitted, therefore, that the above noted deficiencies in the teachings of the During dissertation demonstrate overwhelmingly that no substantive foundation exists upon which to find claims claim 83 and its dependents obvious over this reference.

Although the claims have not presently been rejected as obvious over the During dissertation in combination with any specified prior art teaching, it is also respectfully submitted that no such teachings or combination of teachings have been cited in this case that could cure the deficiencies noted for During. The only other reference raised for obviousness in this action is Goodman, but the teachings of this reference are similarly deficient to that of the During dissertation. When it comes to immunoglobulins, Goodman only mentions expressing immunoglobulin heavy and light chains together in the same cell so that the chains can assemble. Such immunoglobulin, however, clearly does not teach or suggest the single polypeptide invention of claim 83 and its dependents.

Accordingly, because During fails to teach or suggest the claimed invention, claim 43 and its dependent claims and claim 83 and its dependent claims are not obvious under section 103(b) as a matter of law.

REJECTION UNDER 35 U.S.C. § 103 OVER GOODMAN

The rejection of claims 21, 32-54, 56-66 and 68-82 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Goodman in view of Applicant's allegedly admitted prior art is respectively traversed. The rejection is moot as to claims cancelled herein.

Claim 43 and its dependents are not obvious over Goodman

As already mentioned under anticipation, Goodman fails to even mention let alone teach or suggest the requirement for a plant comprising plant cells containing nucleic acid encoding an immunoglobulin single polypeptide product. Goodman's one sentence reference to immunoglobulins sandwiched amidst a wish list of commercially valuable proteins wholly fails to render obvious such claims. Goodman also does not provide any

enablement of such single polypeptide immunoglobulin and is unaware of the requirements for production of any immunoglobulin product in plants.

It is further noted that Goodman's teachings on gamma interferon expression would not reasonably have been considered to advance the possibility of immunoglobulin expression in plants. Gamma interferon is structurally and functionally distinct from immunoglobulin light or heavy chains, the latter of which are immunoglobulin superfamily members. Also, it was known by the late 1980s that antibodies encompassing a heavy and a light chain are secreted through a complex interaction between the chains and other proteins. For example, heavy chain production in B cells was known to precede that of light chain production in ontogeny, and that the heavy chain binds to the BiP protein in the endoplasmic reticulum before heavy chain assembles with light chain. See e.g., Hass et al., Proc. Natl. Acad. Sci. USA 81:7185-7188 (1984) (copy attached as Exhibit B, p.7187, right column, citing reference 11, Burrous et al.. PNAS USA 78:564 (1981)). It was also known that heavy chain production in the absence of light chain production was often fatal in mature B lymphocytes. See e.g., *Id.* (Exhibit B; p.7185, left column). Furthermore, if heavy chain were produced without light chains, the heavy chains were not secreted (see Pepe et al., J. Immunol. 137:2367-2372 (1986); copy attached as Exhibit C, p.2367, left column); The opposite was true, however, when light chains were secreted without heavy chains.

Thus, the absence of a chemical or biological relationship between gamma interferon and immunoglobulin, as well as the known complexity underlying immunoglobulin secretion would have rendered the teachings of Goodman largely irrelevant to the claimed invention. Furthermore, as already discussed, the teachings of Düring do not in any way cure the deficiencies in the teachings of Goodman. Accordingly, the examiner is respectfully urged to withdraw the rejection of claims 43 and its dependent claims as allegedly obvious over Goodman.

Claim 83 and its Dependents are not obvious over Goodman

As already mentioned under anticipation, Goodman also fails to even mention let alone teach or suggest the requirement for a plant comprising plant cells containing nucleic acid encoding an immunoglobulin single polypeptide product comprising the heavy chain or the light chain but not both. Goodman's one sentence reference to immunoglobulins sandwiched amongst is nothing more than a nonenabled wish list.

It is also noted that Goodman's teachings on gamma interferon expression would not reasonably have been considered to advance the possibility of expressing a single polypeptide heavy or light chain separately in plants. As discussed, gamma interferon is structurally and functionally distinct from an immunoglobulin light or heavy chain. Furthermore, it was well known that heavy chains expressed in the absence of light chains were generally toxic to B cells. See e.g., Hass et al., Proc. Natl. Acad. Sci. USA 81:7185-7188 (1984) (copy attached as Exhibit B, p.7187, right column, citing reference 11, Burrous et al.. PNAS USA 78:564 (1981)). One of ordinary skill would, therefore, have been surprised to discover that plant cells could successfully produce a single immunoglobulin chain without toxicity occurring. If this were not the case, then the present inventors' work simply would not have been roundly hailed as a breakthrough in the scientific literature and in the general press. See e.g., cover of Nature, 242(6245), 76-78, 1989 (copy attached as Exhibit D); Excerpt of article in the Los Angles Times (San Diego County), November 2, 1989 (copy attached as Exhibit E).

It is further noted, that assuming *arguendo* that Goodman's limited teachings support to some extent expression of an immunoglobulin single polypeptide in plants, any such teachings would be negated by During attempt and failure to achieve this result for light chains (i.e., During translation, p.80, line 2). Accordingly, in view of the above, it is respectfully submitted that claim 83 and its dependent claims are not obvious over Goodman alone or in combination with any other art of record.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date: March 14, 2002

By _____

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